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Identification of single amino acid residues essential for the binding of lipopolysaccharide (LPS) to LPS binding protein (LBP) residues 86-99 by using an Ala-scanning library.

Reyes O, Vallespi MG, Garay HE, Cruz LJ, Gonzalez LJ, Chinea G, Buurman W, Arana MJ.

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Lipopolysaccharide binding protein (LBP) is a 60 kDa acute phase glycoprotein capable of binding to LPS of Gram-negative bacteria and facilitating its interaction with cellular receptors. This process is thought to be of great importance in systemic inflammatory reactions such as septic shock. A peptide corresponding to residues 86-99 of human LBP (LBP86-99) has been reported to bind specifically with high affinity the lipid A moiety of LPS and to inhibit the interaction of LPS with LBP. We identified essential amino acids in LBP86-99 for binding to LPS using a peptide library corresponding to the Ala-scanning of human LBP residues 86-99. Amino acids Trp91 and Lys92 were indispensable for peptide-LPS interaction and inhibition of LBP-LPS binding. In addition, several alanine-substituted synthetic LBP-derived peptides inhibited LPS-LBP interaction. Substitution of amino acids Arg94, Lys95 and Phe98 by Ala increased the inhibitory effect. The mutant Lys95 was the most active in blocking LPS binding to LBP. These findings emphasize the importance of single amino acids in the binding capacity of small peptides and may contribute to the development of drugs for use in the treatment of Gram-negative bacterial sepsis.

PMID: 11991204 [PubMed - indexed for MEDLINE]

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☐ 1: J Endotoxin Res. 2003;9(5):281-91.

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Inhibition of LPS-responses by synthetic peptides derived from associates with the ability of the peptides to block LBP-LPS interaction.

Arana Mde J, Vallespi MG, Chinae G, Vallespi GV, Rodriguez-Alonso I Garay HE, Buurman WA, Reyes O.

Division of Chemistry & Physics, Center for Genetic Engineering and Biotechnology, La Habana, Cuba. manuel.arana@cigb.edu.cu

The ability of LPS-binding protein (LBP) to greatly potentiate cell responses lipopolysaccharide (LPS) may largely contribute to LPS toxicity in sepsis. The study of agents with the capacity to block the interaction between LBP and LPS might improve the understanding of the role of LBP in Gram-negative infections as well as offering new therapeutic tools for septic disorders. Here we confirm the ability of synthetic peptides comprising the human LBP amino acid region 86-99 to interfere with the LBP-LPS interaction. The analysis of selected alanine mutants of a blocking peptide corresponding to the LBP region 86-99 suggests the importance of peptide amphipathicity for the inhibitory activity. The potency of the native peptide and a selected analogue at inhibiting in vitro and in vivo LPS-induced responses was associated with their relative activity in blocking LBP-LPS interaction. It was remarkable that these peptides were at least 500-fold more active in vivo than in vitro. Also, the inhibitory activity of peptides LBP86-99 and LBP86-99A seems to be independent of LBP concentrations, a behavior that is not relevant for the potential use of these peptides in septic disorders where LBP serum concentrations are considerably elevated.

PMID: 14577844 [PubMed - indexed for MEDLINE]

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